REMARKS

Prior to entry of this Amendment, claims 1, 3-14, and 16-18 of the application were pending. Claims 1, 3-14, and 16-18 have been rejected. In this Amendment, Claims 1, 3, and 13 have been amended. After entry of this Amendment, Claims 1, 3-14, and 16-18 are pending in the application. The claims have been amended to clarify the invention. No new matter is introduced by these amendments. Support for the amended claims may be found in the specification and claims as originally filed. Applicant requests reconsideration of the rejected claims in view of the foregoing amendments and the following remarks.

35 U.S.C. § 112, Second Paragraph

In the Office Action dated February 26, 2003, the Examiner maintained the rejection of claim 1 for reciting the phrase "skin liable to form stretchmarks." Applicant has amended claim 1 to indicate that skin liable to form stretchmarks or having stretchmarks "includ[es] skin of the thighs, abdomen, breast, or a combination thereof." Applicant respectfully contends that claim 1 as amended is fully compliant with 35 U.S.C. § 112, second paragraph, and Applicant respectfully requests that the Examiner reconsider the rejection.

In the Office Action, the Examiner also rejected claim 3 for reciting trademarks. Applicant has amended claim 3 to replace the trademarks with descriptions of the products. Applicant respectfully contends that claim 3 as amended is fully compliant with 35 U.S.C. § 112, second paragraph, and Applicant respectfully requests that the Examiner reconsider the rejection.

In the Office Action, the Examiner also rejected claim 13 for reciting *Enteromorpha compressa*. Applicant has amended claim 13 to recite "an extract of *Enteromorpha compressa*." Applicant respectfully contends that claim 13 as amended is fully compliant with 35 U.S.C. § 112, second paragraph, and Applicant respectfully requests that the Examiner reconsider the rejection.

35 U.S.C. § 103(a)

In the Office Action, the Examiner also rejected all the claims 1, 3-14, and 16-18 as being unpatentable over Rapaport *et al.* ("Rapaport") in view of either Frei *et al.* ("Frei") or Quelle *et al.* ("Quelle") (further in view of additional references). The Examiner states that the Rapaport reference lacks a fermented soya peptide or a tripeptide. However, the Examiner states that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to add the fermented soya peptide of Frei et al...because Frei et al. is drawn to a method of increasing firmness, elasticity, and tone." Further, the Examiner indicates that it would have been obvious to combine Rapaport and Quelle, which teaches a Gly-His-Lys tripeptide, "to achieve[] a composition that treats stretchmarks and decreases the signs of aging." Applicant respectfully traverses the rejection because one skilled in the art would not be motivated to combine the teachings of Rapaport with either Frei or Quelle to achieve "[a] method for reducing the formation of and/or treating skin stretchmarks," as recited in the pending claims.

While Rapaport teaches a method of treating stretchmarks, Frei teaches a method of treating skin aging, and in regard to skin care, Quelle teaches tripeptides as anti-aging factors. One of ordinary skill in the art would recognize that skin stretchmarks and skin aging have distinct etiologies. For example, please see the enclosed study prepared by the inventor that compares striae distensae and cutaneous aging, and see also the enclosed article entitled, "The Cause of Striae Distensae," Sam Shuster, *Acta Dermatovener*, p 161-169. Because striae distensae and cutaneous aging have distinct etiologies, one skilled in the art would not be motivated to use anti-aging agents to treat stretchmarks. Merely because one skilled in the art might use similar indicators to assess the efficacy of anti-stretchmark agents and anti-aging agents, (such as increasing firmness, elasticity, and tone), it does not necessary follow that one skilled in the art would be motivated to use anti-aging agents to treat or reduce the formation of stretchmarks.

Further, references in the art indicate that anti-aging agents are not efficacious at treating stretchmarks. Please see the enclosed article entitled, "Low-Dose Tretinoin Does Not Improve Striae Distensae: A Double-Blind, Placebo-Controlled Study,"

Pribanich *et al.*, *Therapeutics for the Clinician*, (1994), 54:121-24. As shown by the title, tretinoin, which has been used "[i]n the treatment of extrinsic aging of the skin," is not effective at treating stretchmarks. As such, anti-aging agents are not necessarily efficacious at treating stretchmarks, even though one skilled in the art might use similar indicators to assess the efficacy of anti-aging agents and anti-stretchmark agents. Therefore, an increase in firmness, elasticity, and/or tone merely indicates that the anti-aging agent or anti-stretchmark agent may be efficacious at treating the underlying etiologies. However, where the underlying etiologies differ, as do the etiologies of striae distensae and cutaneous aging, and where references in the art teach that anti-aging agents are not efficacious at treating stretchmarks, one skilled in the art would not be motivated to use anti-aging agents to treat strectchmarks. As such, Applicant respectfully contends that it is improper to combine Rapaport with either Frei or Quelle in a rejection under 35 U.S.C. § 103(a), and Applicant respectfully urges the Examiner to reconsider the rejection.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

Applicant previously responded to a rejection under 35 U.S.C. § 112, first paragraph, in the Office Action dated July 3, 2002. The Examiner has indicated that Applicant's previous amendment and remarks are sufficient to overcome the rejection. However, in further support, Applicant has enclosed herewith an article entitled "Cosmetic Cream May Prevent Striae Gravidarum," Cheryl Guttman, *Cosmetic Surgery Times*, November/December 2002, p. 11.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 06-1447. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 06-1447. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby

petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 06-1447.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date 6/26/03 By _____

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STRIAE DISTENSAE	CUTANEOUS AGING
- Young people: 50 % - puberty : 25 % girls 10 % boys	- Old people
- Well defined areas (abdomen, breast, buttock, hips, shoulders, knees)	- Diffuse, maximum cutaneous aging in photo-exposed areas
- 50 to70 % primipara , around the umbilical areas	
- Not natural	- Natural process, intrinsic aging: shortening of telomeres
- Predisposing factors: internal diseases - . any raise of systemic or local steroids (obesity, Cushing, local steroids, stress) . infectious diseases with fever . Marfan's syndrome: genetic disease alteration of elastic fibrillins . No role of external factors (except local steroids)	- Extrinsic predisposing factors: sun exposure pollution, cigarette smoking
- Acute	- Chronic
- Clinical aspect : red striae, white scars	- Clinical aspect : deep furrows, dryness, atrophy
- Pathophysiology . damages to fibroblasts induced by acute inflammations: blockage of macromolecule synthesis, reduction of RNAm coding for collagens I and III and fibronectin . **Role of mast cells :** Increase of eosinophilic tissue, Increase of elastase by macrophages, Increase of inflammatory cytokines IL1 ...	- Pathophysiology .intrinsic aging: slow reduction of fibroblast functions .extrinsic aging : aggressions to fibroblasts or to dermal fibers
- Increase of steroids	- No role of steroids, decrease of estrogens speeds the process
- steroids : Decrease of collagen synthesis by fibroblasts catabolism of cells cofactor of elastase, collagenase (MMP)	- No acute inflammation, no role of mast- cells Increase of MMP idem
- Role of mechanical stress . striae perpendicular to major traction forces . fibroblasts → myofibroblasts → reparation (via TGFβ)	- No role of mechanical stress (some for wrinkles)

- Increase of IFN Gamma
- Decrease of TGFβ

- Increase of AP1 (sun)
- Decrease of TGFβ

STRIAE DISTENSAE ARE NOT A MODEL OF LOCALIZED AGING

HISTOLOGY

STRIAE	AGING
RECENT STRIAE	
- Massive inflammatory infiltrate (macrophage, histiocyte, lymphocyte)	- No inflammatory infiltrate
- Neoformation of fine elastic fibers	- No neoformation of fine elastic fibers
LATE STRIAE	
- Slight or no epidermic alteration	- Epidermic alteration
- dermal atrophy 50 % - Decrease of procollagens I and III, fibronectin	- Slower and milder dermal atrophy - Decrease of procollagens I and III, fibronectin
- Decrease of «fibrillin»	
- Decrease of elastic fibers of papillary dermis disorganised elastic network. After degradation, elastic fibers could be re-synthesised , multiplied and bigger and reorganised parallel to BMZ.	- diffuse decrease of elastic fibers or solar elastosis
ECHO : sharp demarcation between striae and normal skin - atrophy - hyper echogenicity with dense linear lines not well oriented with BMZ (=elastic fibers)	- Idem for wrinkles - Hypo echogenicity (Grenz zone)

S. SHUSTER HYPOTHESIS : a certain amount of collagen « cross-linkage » is mandatory for striae.
If no cross link (Marfan) → very extensible.
If many (aging) →skin breaks.
In between→Striae distensae.

STEROIDS	
- Steroids change the physical properties of collagen rather than its quantity	- Total decrease of collagen . less resistance to stress but aging does not induce striae

Why steroids may provoke striae at a middle age? Because they impair the ratio between rigid collagen (cross-linked) and elastic collagen (not cross-linked) and make it more similar to the ratio of young people able to develop striae

Action of TOPICAL RETINOIDS

- The only controlled study shows clinical but no
- histological improvement after 2 months
- Major action on cutaneous aging

CONCLUSION

- Some intermediate mechanisms are similar	Increase of MMP Decrease of TGFβ Decrease of collagen
- But initial factors are different	acute inflammation in striae acute aggression of fibroblasts role of steroids role of mechanical tension
- Final results are different	very localized striae different topography persistence of disorganised elastic fibers role of mast-cells fibroblastes have different contractile properties

STRIAE DISTENSAE ARE A MODEL OF PATHOLOGIC SCARRING

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THE CAUSE OF STRIAE DISTENSAE

Sam Shuster

Department of Dermatology, University of Newcastle upon Tyne

Abstract. Striae are always initiated by stretch whether the stretch is excessive or minimal: spontaneous striae do not occur. Cross-linkage of collagen appears to be more important than amount of collagen in permitting striae in response to stretch. An increase in cross linkage as in age increases the resistance to stretch deformation, but this rigidity leads ultimately to tearing of the skin and not striae. At the other extreme, the absence of crosslinkage leads to "elasticity" and excessive stretching with eventual rupture of the skin if the stretch goes beyond the elastic limit, but again, no striae. Striae appear to occur therefore only in skin in which the connective tissue is partially mature with a critical titre of rigid cross-linked collagen and "elastic" unlinked collagen thus permitting a limited degree of stretch and a limited intradermal rupture, i.e. striae. (Although rigidity and elasticity are presented here in terms of collagen cross-linkage it seems probable that changes in interfibrillary materials such as glycosaminoglycans will prove important in this respect). This balance of stretch and limited tear is a continuous process and is an adaptation to the needs of growth in adolescence and change in body mass in early adult life and there are many many subclinical "striae" for each gross tear which is recognised clinically. An important factor likewise appears to be rate of stretch since if it is very slow, striae are less likely; there is "give" and new collagen formation. Although this working hypothesis is consonant with the facts only further work will show whether this smooth consonance is that of the fable or the weathered rock of fact.

Key words: Striae; collagen; Cross-linkage; Elasticity.

The question I wish to consider is "what is the cause of striae?" and immediately I would like to rephrase the question. Both philosophers and scientists like to rephrase questions, but for different reasons: the philosopher rephrases to establish yet another unverifiable answer but the scientist rephrases questions in order to pose a testable and therefore disposable hypothesis. My rephrasing of the question is in the title "the cause of striae *distensae*" – in other words, my working hypothesis is that all striae are a response to stretch whether the stretch is gross and obvious or trivial and undetected – so called "spontaneous" striae. Nothing in life is spontaneous; what is miscalled "spontaneous" striae occur when the stimulus/response setting is low so that the stretching stimulus is less apparent than the "strial" response. It follows from the hypothesis implicit in my rephrasing that my primary question is why does stretch cause striae? In examining this question it is helpful to consider first of all the question of "why not?" In other words what are the alternatives to striae?

Skin is a dyshomogeneous tissue and a stretching force can produce three responses in it:

1) a reversible elongation, i.e. an "elastic" stretch response;
2) a failure to elongate, ultimately with a tear, i.e. an "inelastic" rigid response with ultimate brittleness;
3) a mixture of the two responses with a limited "elastic" stretching response and a limited rigidity, with a limited tear

This third response is the situation with striae.

What decides which of these three processes will occur? The resistance of the skin to deformation lies mainly in its dermal collagen and the two main controlling factors are 1) the quantity of collagen and 2) the quality – notably the degree of cross linkage between individual , molecules, though the role of interfibrillary material must still be regarded as open (see below). In general, the greater the amount of collagen, the greater the resistance to stretch deformation. The same is true with cross linkage; the more the cross linkage, the more the resistance to stretch deformation. This is shown diagrammatically in Fig. 1.

1. *Quantity of Skin Collagen*

Let us examine the amount of skin collagen first. Fig. 2 shows the relationship of collagen content of forearm skin (extensor surface) to age and sex. Skin collagen content on other sites is shown in Fig. 12. It can be

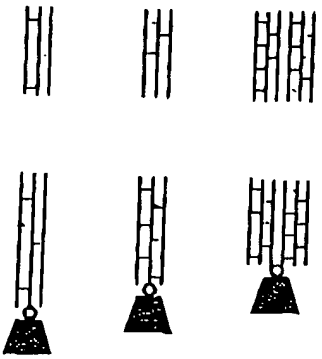

Fig. 1. The influence of quantity of collagen and degree of crosslinkage on the response to a stretching force. The possible role of interfibrillary material is discussed in the text.

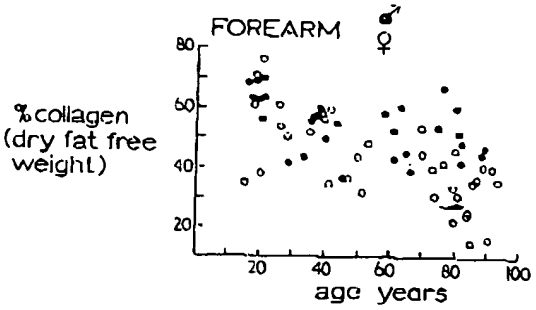

Fig. 3. Skin collagen from same data as Fig. 2 plotted in relative terms (as %). There is no significant change with age in the males despite the clear progressive difference when the data is plotted in absolute terms (i.e. relative to skin surface area, figure 1).

seen that there is a roughly 1% per year decrease in skin collagen with age and that at all ages, men have more collagen than women. In this respect women are about fifteen years older than men throughout their life, thus confirming my long held view that our Maker was a male chauvinist. There has in the past been much controversy as to the quantitative changes in skin collagen with age. It is mostly artefactual. Work which purports to show no change in collagen with age, or indeed, an increase with age (6) is in error and the error is due to the incorrect expression of skin collagen as a percentage. It is extremely dangerous to express a constituent of a tissue (particularly a non-homogenous tissue such as skin) as a percentage since an apparent change in that constituent may equally well be due to changes in content of the other constituents. Thus there is little age change in relative collagen content (e.g. %) of male forearm skin (Fig. 3) despite the large changes which occur in *absolute* quantities (Fig. 2). For this reason we evolved the method of expressing skin collagen content in relationship to skin surface area (as shown in Fig. 2) (9, 10). This mode of expression is the most direct answer to the question of what is the collagen content of a given piece of skin. The same mode of expression can be applied both to skin constituents and events and it is pleasing to note that other authors are now using it even though they rarely acknowledge its origin!

Now the greater the skin collagen content the greater the resistance to stretch. But if skin collagen *content* was the sole determinant of resistance to stretch striae

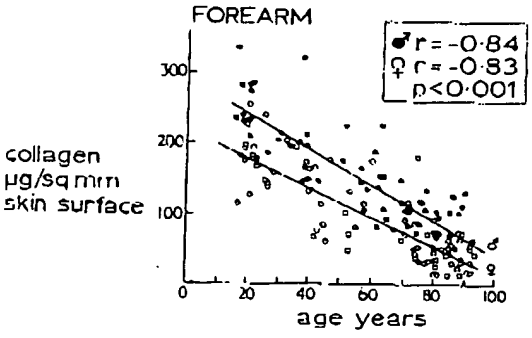

Fig. 2. Total skin collagen content (mid point of extensor aspect of the forearm) to show the progressive decrease with age and the greater content in males.

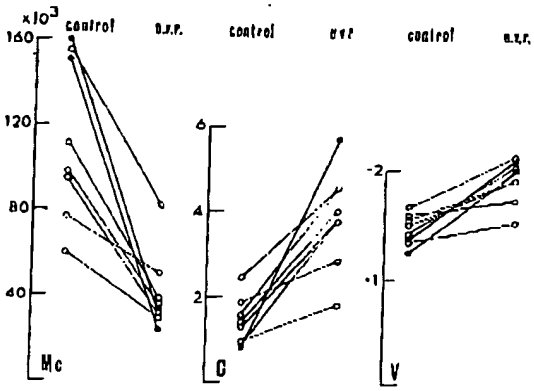

Fig. 4. The increase in cross linkage produced by UVB irradiation in vitro in hairless mouse skin (1). Mc=mean molecular weight/cross-linked chain segment; C=number of cross-links per molecular weight of 300,000; V=volume of dry material/water wet material at 65°C.

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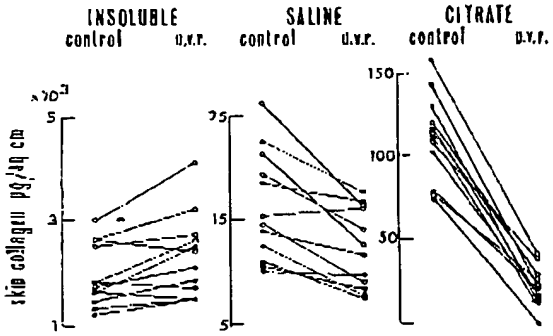

Fig. 5. The decrease in soluble and increase in insoluble collagen fractions produced by UVB irradiation in vitro in hairless mouse skin (10) collagen is expressed as µg hydroxyproline/g of half pelt and the lines join irradiated with non-irradiated half pelt from same animal.

would be expected to occur increasingly with age as skin collagen content decreases. In fact, striae are a feature of puberty and early adult life but not of old age. For example, ascites in early adult life produces striae, but ascites in later life simply stretches the abdominal skin even though there is much less collagen in the skin with age. We can therefore exclude collagen content as a sole determinant of striae and look at other qualities of collagen which may modulate the response to stretch, e.g. cross-linkage.

2. *Cross Linkage of Collagen*

There is a progressive increase in inter-molecular cross linkage of skin collagen with age. This has been shown many times both chemically and by secondary properties such as thermal contraction, the force of which increases progressively with age. A similar effect can also be shown with the experimental model of ultraviolet irradiation (UVB) which increases the cross-linkage in collagen (3) (Fig. 4). Thus there is conversionof the less crosslinked and more immature saline and citrate soluble collagens (Fig. 5) to a more cross linked stable and insoluble form. This can be shown both by irradiating the skin in vitro or by irradiating the whole animal in vivo (11). The way in which UVA accelerates this cross linkage process is not yet clear. Now a stretching force applied to UVA cross linked collagen produces much less deformation, that is that it is far less elastic. This is shown in Fig. 6 which is skin of a hairless mouse before and after irradiation with UVA in a dose sufficient to increase the number of cross linkages.

The clinical evidence of the effect of cross linkage on the response to a stretching force is, like that of total collagen content, quite clear. If we look at skin in which there is little or no cross linkage in the collagen, e.g. some of the forms of the Ehlers-Danlos syndrome, a stretch force leads to an excessive skin extension; thus because of the increased "elasticity" the skin stretches rather than develops striae. If the stretch is very excessive then the skin having reached its elastic limit will eventually rupture. By contrast, in the skin of the elderly, because of its increase in cross linked collagen there is less stretch once the initial slack is taken up and there is early and total rupture of the collagen fibres as the skin rapidly reaches its elastic limit. Thus just as in skin with uncrosslinked collagen the whole skin tears without striae formation. This is shown on the right of Fig. 7 which is the skin of the forearm of an elderly patient where a shearing force of quite moderate intensity led to tear of the *whole* skin. The easy production of a tear despite increased collagen cross linkage is of course due to the great decrease in total collagen content with age (Fig. 2). This is the basis of the stellate scars commonly seen in the forearm skin of the elderly (8, 13).

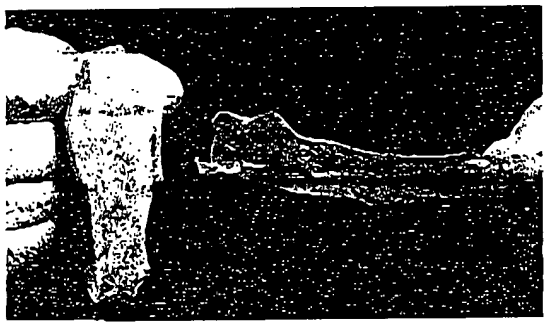

Fig. 6. The control and UVB irradiated half pelts (from Fig. 5) to show the difference in physical properties. After UVB the pelts become harder and less flexible.

The Cause of Striae

Thus the response to stretch does not lead to striae when the collagen has few cross-links as in the very young or certain diseases, nor when the collagen is very cross-linked as in the aged. In the intermediate stage of life, that is in the young adult there is a slow "give" of the skin with an extending force because there is both rigid cross linked collagen and the more elastic immature collagen. In this situation there is partial stretching and partial tearing. Consequently some of the

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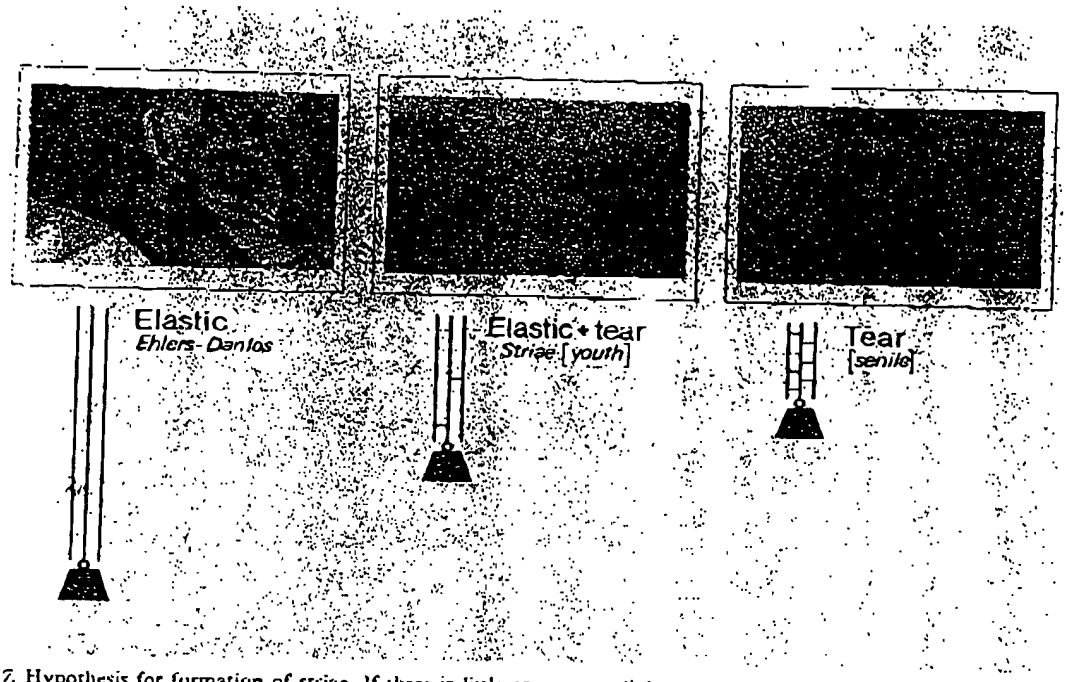

Fig. 7. Hypothesis for formation of striae. If there is little or no cross linkage the skin just stretches and ultimately tears when the skin reaches its elastic limit – the situation in Ehlers-Danlos syndrome. If the skin collagen is very cross-linked as in age, it stretches less and tears sooner. Striae do not occur in either of these two extreme situations, i.e. few cross-linkages or a gross excess of cross-linkages. They occur only between these two extremes. In this state there is partial cross linkage which allows slow stretching and slow tearing. In other words, striae occur when there is a critical titre of cross-linked rigid collagen and immature elastic collagen.
(It is probable (see text) that a change in non collagenous materials such as glycosaminoglycans may also contribute to elasticity and will have to be incorporated into the basic hypothesis.)

fibres will tear, yet the whole skin remains intactthence striae. This process is summarised in Fig. 7.

In summary then striae are due to partial stretching and partial intradermal tearing due to a critical titre of cross-linked rigid collagen and immature elastic collagen. This combination gives both the elastic and rigid support necessary for growth and if growth cannot be encompassed by stretch then striae, which are simply intradermal tears are a further method of adaptation to the needs of growth. Although I have equated rigidity with cross-linkage the hypothesis can be extended to include the possibility that interfibrillary material may lead to similar changes in extensibility (see below).

It seems probable that this process occurs continuously during growth and mostly results only in microscopic or very minor intradermal tears which are not detectable as clinical striae. My reason for suggesting this is that it is only the larger intradermal tears which are recognised clinically as striae, yet it is possible to see numerous fine "striae" of all gradations of size most of which go unnoticed. Thus the clinical striae of puberty are the gross and dramatic exteriorisation of a continuous stretch and tear process of growth.

A brief word on elastic tissue which many consider to play a part in the formation of striae. The function of elastic tissue is unclear but I know of no evidence that it has any special part to play in the elasticity of skin. Skin elasticity could be explained perfectly adequately by collagen itself. On existing evidence the term "elastic" fibres is a misnomer and there is no evidence of a special relationship to striae.

My hypothesis has not yet lived through the luxury of formal proof; like uncrosslinked collagen it is still young. Thus it retains the advantage of flexibility but the defects of as yet untested firmness. Let us now test it against some of the known facts.

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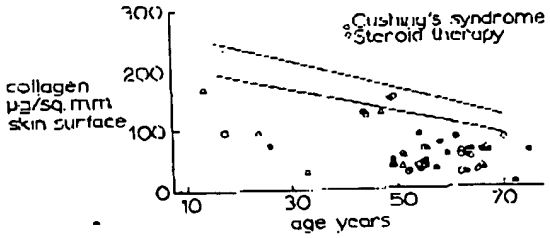

Fig. 8. The decrease in absolute skin collagen content from exogenous or endogenous glucocorticosteroids. The closed symbols are male and the open female; the upper line is the mean normal for males and the lower for females.

1. *Corticosteroids and Skin Collagen*

Corticosteroids reduce total skin collagen content (12) (Fig. 8). This occurs whether the corticosteroids are given by mouth or topically. Much nonsense has been written about an alleged special role of fluorinated corticosteroids in this respect; but the evidence (poor though it is) relates the decrease in skin collagen *solely* to the "anti-inflammatory" potency of corticosteroids regardless of their chemical structure. (Whether new corticosteroids can be developed which dissociate anti-inflammatory and collagen atrophy potencies still remains to be shown). Fluorination is irrelevant and collagen atrophy occurs with "natural" steroids such as hydrocortisone in Cushing's syndrome (Fig. 8) (1), when they occur in high concentrations. There is an almost equally uncritical volume of work which equates this action of corticosteroids with the decrease in skin thickness which we described (1). This is totally unwarranted because the acute changes in skin thickness after topical corticosteroids are small in degree and occur too rapidly to be due to the gross changes in skin collagen which we found. Moreover dermal thickness and collagen content can only be correlated in certain circumstances (9). Finally skin thickness may be restored after stopping corticosteroids but it has not been shown that collagen can be restored likewise. For these reasons it may prove dangerous to correlate the "skin thinning" potency of corticosteroids in a short term assay with the long term and serious effects on total skin collagen. (Use of the term "atrophogenic" for this short term thinning has served only to confuse the issue).

As we have already shown in aged skin the decrease

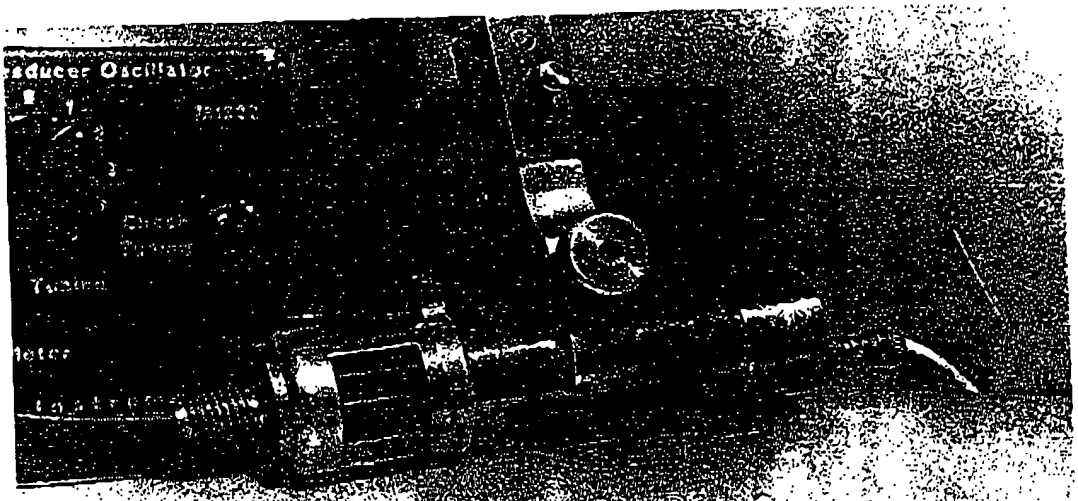

Fig. 9. Head-of-stretch-strain device (4) resting on two feet which are stuck to the skin surface. The two feet are driven apart at a fixed rate and the stretch is measured by a strain gauge. The stretch strain curve is plotted on an X-Y recorder.

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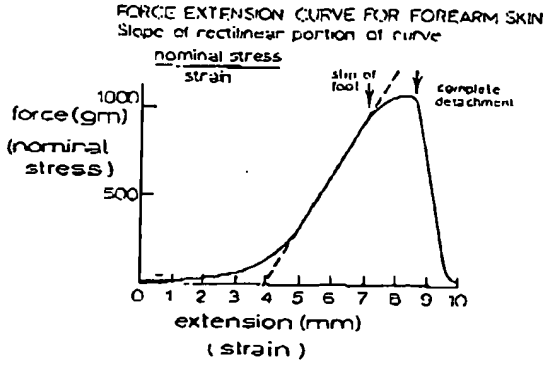

Fig. 10. Typical stretch-strain curve from normal forearm skin. There is an initial period when the slack is taken up followed by a linear curve and finally a flattening with a rapid fall off as the keratin shears. The slope of the linear part of the curve is the nominal stress/strain which is proportional to Youngs Modulus and is used to measure the elasticity of skin.

in total collagen will not by itself lead to striae although it will inevitably decrease the resistance to stretch. So what is the explanation of corticosteroid striae? Again the evidence is of a change in the physical properties of the collagen rather than its quantity We first suspected this in the course of a study of alopecia totalis. We found that in a few of these patients, very very high single doses of corticosteroids intravenously will occasionally initiate regrowth of hair, an observation of great theoretical interest and negligible practical consequences which is discussed further elsewhere, (5). Now one of our patients developed many striae within days of such treatment. Whilst it is not yet certain to what extent the decreased collagen found

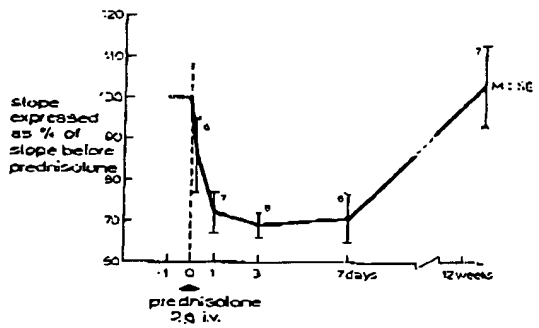

Fig. 11. The effect of a single large intravenous dose of prednisolone on linear elasticity of skin. Skin elasticity increases in the first 24 hours of the glucocorticoid and recovers after one week.

after corticosteroid is due to impaired synthesis or increased degradation of collagen, a few days is too fast to cause a significant loss of collagen by either process. We therefore considered the possibility that some critical change in its quality such as that due to cross linkage would lead to an immediate alteration in the response to stretch. To study this, we used an instrument which we specially designed to study stretch strain characteristics of normal skin in vivo (4). The instrument (Fig. 9) has a driving head which moves two feet apart at a preselected rate to produce a controlled stress. The two feet are stuck to the keratin with "Eastman 910 Adhesive" and the consequent stress strain is measured as the rate of deformation using a strain gauge with a direct readout onto an X-Y recorder. A typical stretch/ strain response is shown in figure 10. There is a slow rise as slack is taken up, a linear portion where strain matches stress followed by a flat part when the stratum corneum begins to tear. The slope of the linear portion is mainly a measure of the stress/strain characteristics of the dermal collagen. To our great surprise we found a very rapid response to a single large intravenous dose of the corticosteroid (Fig. 11) with a great decrease in the resistance to a stretching force. Whilst the mechanism for this rapid and dramatic change is completely unknown it seems unlikely for reasons already discussed that it is due to any change in quantity of collagen. Although there is no known action of corticosteroids on collagen cross linkage which occurs so rapidly I do not believe that this possibility has been seriously studied experimentally. It should also be pointed out in this respect that the nature of at most half of the cross links in collagen has been established. It is perhaps more likely there is some other, as yet, undefined mechanism for interfibrillary adhesion upon which the corticosteroids act and it is the authors view that with the current interest in cross-linkage the role of interfibrillary materials such as glycosaminoglycansin promoting rigidity and elasticity may have been neglected.

Thus corticosteroid striae appear to be related to a critical change in the resistance of collagen to stretch. This change is brought about by a process *akin* to a reduction in cross-linkage (how much due to cross-linkage and how much to changes in interfibrillary material remaining an open question) and together with an absolute reduction in the quantity of mature, stable and rigid cross-linked collagen. Thus it seems likely that the reason that corticosteroids can initate striae formation in the skin of the middle-aged is that it

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induces a process which alters the ratio of rigid (? stable and cross-linked) to elastic (? uncrosslinked) collagen so that as in the normal situation in younger individuals one has again the critical balance of rigidity and stretch which is essential for the production of striae.

2. *Puberty and Pregnancy Striae*

(a) Puberty Striae

Despite the common view I know of no evidence that puberty striae are in any way caused by a specific endocrine action on collagen and it seems to me that stretching of a semi-mature collagen is a perfectly adequate explanation for the striae of normal puberty. At this time there is an increase in girth from muscle, fat and bony growth. Again there may be a disproportionate growth spurt in one part of the body. This anecdote of one of my patients who presented with the rapid onset of striae around the shoulders makes the point. He was a young man who had left a very sheltered home life and ran away to sea. He rapidly developed his shoulder girdle muscles in the course of his new and strenuous activities as a merchant seaman! This young man noticed he would develop his fresh striae during particularly intensive bouts of muscular activity. Thus local stretch produced local striae. This is the clue to the disparate appearance of striae in different individuals and as well as their different sites of appearance. Thus the "conifer tree" pattern of striae on the back (Fig. 7) is usually to be found in individuals who have had a sudden spurt of growth in the vertical height of their trunk. This example illustrates well how the clinical problem of stretch striae arises from the disparity between the factors which set body mass and those which set limits on the amount and properties of the material covering it. In other words, we may be provided with too little wrapping for our bodily parcel (too much leads to Eairts syndrome, which is the converse and not often recognised). Our genes for skin connective tissue quantity and quality may be inappropriate for the load imposed upon it:- thus while height is polygenic, all too often girth is polyphagic and the skin has to accommodate to it. Or again in the case of our patient with conifer-tree striae, back length may have been contributed by grandmother and back and back skin by grandfather; thus the family incompatibilities had been argued out along our patient's back.

Skin collagen content appears to be a characteristic of the individual and that is why I assume it to be under genetic control. My evidence for this is shown in Fig. 12 which gives the collagen content of a number of different sites. It is apparent that although the skin collagen content varies in different parts of the body, this variation is consistent from individual to individual. Thus there is a site-specific characteristic to the skin collagen content. Equally there is a difference which is characteristic of the individual. Thus if you have a lot of collagen in one region you will have a lot of collagen in all regions, and conversely (Fig. 13). In other words, the quantitative setting of your skin collagen is both individual and site-specific and the control of this is presumably genetic. Presumably the same is true of relevant biochemical and physical properties. It seems more than likely that faced with the great variety of genetic and non-genetic factors which determine body mass, the skin's own genetic setting for collagen is often inappropriate. This disproportion between the genetic setting for skin and body bulk may be further accentuated by the extent and variety of acquired changes in body bulk. Thus

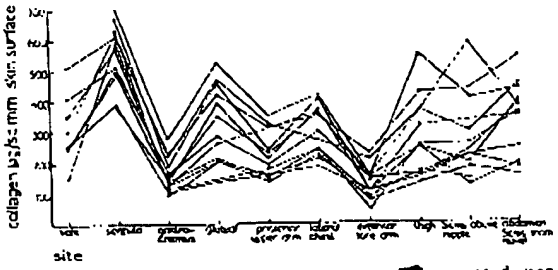

Fig. 12. Absolute skin collagen content (expressed per unit of skin surface area) taken at post mortem from different skin from 12 individuals. The lines join the values for skin samples from the same individuals. With the exception of breast and abdomen in a few individuals, the collagen content of skin from each area was a characteristic of that area.

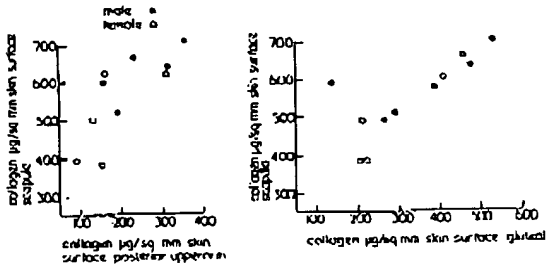

Fig. 13. The inter-relationship between collagen content in different parts of the body. Scapular region is plotted against skin from posterior upper arm and gluteal region from data in Fig. 12.

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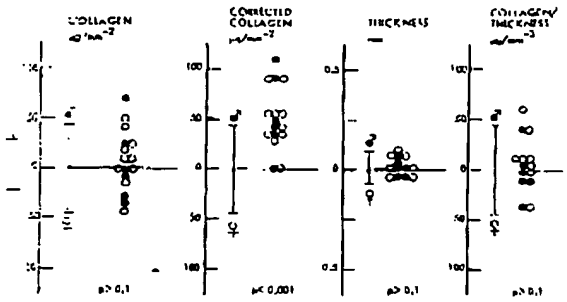

Fig. 14. Skin collagen, skin thickness and collagen density in obesity (2). Total skin collagen is expressed both as a function of actual surface area of the biopsy and as the calculated "ideal" surface area from which the skin will have stretched during weight gain (from ideal body weight/body surface nomogram). Thus the first column shows skin collagen to be normal despite stretching of the skin by obesity. The increase in skin collagen necessary to maintain this response to stretching is shown in the second column. In this way skin thickness and collagen density are maintained (second and third columns).

whether an inappropriate body mass derives from exogenously primed growth of muscle or fat or an endogenous growth spurt, the skin has to cope with this.

Now if the accretion of body mass has been slow new collagen formation appears to be able to keep pace with growth in the stretched skin. Thus in obese limbs we have shown that total skin collagen keeps pace with the extension of the skin surface area by obesity (Figs. 14 & 15). Presumably this process occurs also in

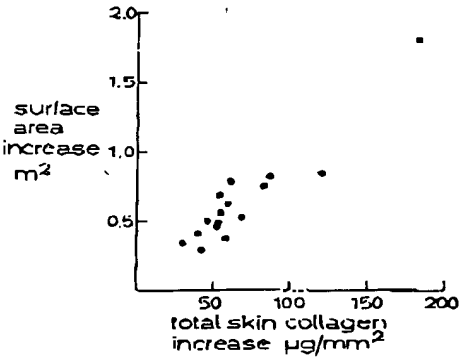

Fig. 15. The increase in skin collagen from the second column in Fig.14 plotted against the increase in body surface area to show that skin collagen content keeps pace with skin stretching in obesity.

programmed growth. This is not the case when the extension is rapid where the consequence is a tear in the elderly or striae in younger individuals as we have already seen (Fig. 7). Thus an important factor appears to be the rate of application of force. A slow application of force, at any rate in early life, is accompanied by an increased growth of collagen. A more rapid stretch leads to one of the three responses of stretch, tear or striae. (b) Pregnancy Striae.

Whereas it is possible that one or more hormones of pregnancy alter the intermolecular cross linkages or physical adherence between fibrils of collagen this has not been shown to be the case. I suspect that stretch in a young adult who possesses the perquisite of a critical titre of rigid and elastic collagen will prove an adequate explanation along the lines I have already proposed (without evoking an endocrine induced reduction in cross-linkage or interfibrillary adhesion.

3. *Tuberculosis and Acute Disease*

The striae which used to be seen in acute tuberculosis and similar diseases resemble those of acute corticosteroid action where the response of striae occurs with minimal stretching force. Although the increased secretion of cortisol which occurs in these situations may provoke the critical change in collagen elasticity other endocrine and metabolic changes (including an altered local response) have not been excluded. Thus skin collagen content decreases with inanition – and I have seen "collagenolytic" or shear purpura, (i.e. like the purpura of lichen sclerosus, Ehlers-Danlos syndrome and primary amyloidosis (8) and first shown for senile and corticosteroid purpura (7, 13) on the breast skin in anorexia nervosa. It is not known whether there is a parallel decrease in cross linkage or a change in extrafibrillary material and this would merit further study.

4. *Marfan's Disease*

Insufficent is known about Marfan's Disease to know whether the striae which occur in this condition are associated with a critical combination of cross linked and uncrosslinked collagen which I have proposed as the underlying feature of susceptable skin.

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THERAPEUTICS FOR THE CLINICIAN
NEW REPORTS ON TREATMENT MODALITIES OF
POSSIBLE INTEREST TO PATIENT-CARING PHYSICIANS

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Low-Dose Tretinoin Does Not Improve Striae Distensae: A Double-Blind, Placebo-Controlled Study

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Friday G. Simpson, MD, Huntington, West Virginia
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Striae distensae occur on the abdomen and/or breast in 90 percent of all pregnant women and are the result of extrinsic and intrinsic factors. This study investigated the response of pregnancy-related abdominal striae to treatment with tretinoin cream (0.025 percent) applied daily for seven months. In this study, eleven subjects were randomly assigned to tretinoin or placebo treatment groups. Before and after photographs were evaluated by a standardized system. There was no difference or improvement in the treated group compared with control subjects. Tretinoin 0.025 percent cream was ineffective in improving striae distensae in these subjects.

Tretinoin (Retin-A®), a vitamin A derivative, is a prescription cream used to treat acne. A recent review of potential therapeutic applications of this agent includes altered keratinization disorders, infectious/inflammatory disorders, keloids and hypertrophic scars, mucocutaneous disorders, pigmentation disorders, and malignant and premalignant disorders.[1] In the treatment of extrinsic aging of the skin (eg, environmental photoaging), tretinoin has been shown to reverse these processes at the cellular level. In a double-blind study, Weiss et al reported that after sixteen weeks of topical treatment with tretinoin, visible reversal of wrinkled and aged skin occurred.[2] When tretinoin was applied to keloids and hypertrophic scars, there was improvement in the scars' appearance, pain, and size.[3]

REPRINT REQUESTS to Bowman Gray School of Medicine, Department of Family and Community Medicine, Medical Center Boulevard, Winston-Salem, North Carolina 27157-1084 (Dr. Pribanich).

To date, only one study has investigated the efficacy of tretinoin cream for the treatment of striae distensae. In that study, 0.1 percent tretinoin cream was applied to striae distensae of various ages for three months in a nonrandomized manner with no control group.[4] Although the results were favorable, the experimental design was flawed. How the 0.1 percent tretinoin cream strength was chosen over less potent/irritating tretinoin creams was not reported. However, a dose-response relationship was mentioned, with 0.1 percent cream as "most effective," but this was not objectively defined.[4] These positive results could be related simply to the irritant effect of the cream rather than the agent's action on dermal fibroblasts.

Our study explored the treatment of striae distensae on the abdomen with tretinoin cream. The study was a double-blind prospective design that used 0.025 percent tretinoin cream, since it is the least irritating form.

Materials and Method

Thirty-two women with abdominal striae volunteered from a university-based obstetrics/gynecology clinic and private community obstetrics/gynecology practices. All subjects agreed to use contraception for the duration of the study. The majority of the subjects who did not complete the study could not be contacted after the initial visit despite intensive attempts at follow-up. No attempt was made to limit participants based on age, age of striae, causes of striae, or grade of striae (Table I).

The design of the study was a double-blind placebo-controlled prospective protocol approved by the University's Institutional Review Board. Selection of the treatment and placebo groups was made using a table of randomized numbers.[5] A person not associated with this study assigned these numbers and dispensed the cream. Subjects in the treatment group received unmarked tubes of tretinoin (0.025 percent) Retin-A® in a standardized vehicle cream. The placebo-treated group received the same standardized vehicle cream, in the same unmarked tubes, but without the tretinoin medication. Cream was applied each evening,

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TABLE I
SUBJECTS WITH STRIAE DISTENSAE

Age of Patients	Age of Striae	Color of Striae	Location of Striae	Cause of Striae	Grade of Striae (Before/After Treatment)	Improvement per Patient Report	Weight Gain/ Loss (kg)
18	2 to 3 yrs	white	abd	pregnancy/obesity	4/4	yes	–0.45
27	6 mos	white	abd	pregnancy	4/4	yes	+7.65
22	2 yrs	pink	abd	pregnancy	4/4	no	–2.48
27	2 wks	violet	rt. hip	pregnancy	4/4	yes	–5.85
28	8 yrs	pink	abd	pregnancy	4/4	no	–1.80
23	2.75 yrs	pink	abd	pregnancy/obesity	4/4	no	–0.9
30	5 yrs	pink	abd	pregnancy	4/4	no	+1.58
18	1.5 yrs	white	abd	pregnancy	4/4	no	+0.9
19	3 to 4 wks	white	lt. hip	+wt	4/4	yes	–4.50
26	2 wks	violet	abd	pregnancy	4/4	yes	–1.80
31	13 yrs	white	abd	pregnancy	4/4	N/A	+6.75

Abd, abdomen; rt. hip, right hip; lt. hip, left hip.

after bathing, to the prescribed area. Avoidance of other skin lotions, creams, and sun exposure was emphasized.

Photographs of an 8.5 by 8.5 cm treatment area on the left infraumbilical region were taken in all but two subjects. These two exceptions had no striae in that location, but had them instead on their hips. The hip with the most striking lesions was selected, documented, and treated. Patients' weights were obtained and monitored for the duration of the study.

The treatment area was photographed in a standardized manner with lighting, distance, and film development the same for each subject during clinic visits. A Kodachrome 64 camera was used with a built-in flash and camera stand utilizing KR-126 color slide film. "Before" treatment photos were used as landmarks for follow-up photography at eight months.

Visits were scheduled at one month, two subsequent three month intervals, and at the eighth month following study initiation.

Striae distensae were graded in the 8.5 by 8.5 cm area as to severity as outlined in Table II. All subjects had grade 4 striae at the beginning of the study. Judging was done by review of the photographs by three board-certified dermatologists. All slides were reviewed independently by the dermatologists to assess changes. The dermatologists were blinded to the subjects' treatment groups. Percentage changes in width, length, number, and color, and improvement in texture and/or appearance of skin were evaluated and quantified. "Before" and "after" slides were shown side-by-side for comparison during the dermatologists' evaluations. The subjects were also asked for their impression of improvement at the treated sites on an exit questionnaire.

Statistics

The Pearson correlation coefficient (r) was used to calculate interrater reliabilities between dermatologists. Data obtained from the dermatologists' questionnaires was analyzed using the analysis of variance F test. Data from dermatologists' questionnaires was analyzed separately for each group, and analyzed as collapsed data across dermatologists. All p values are two-sided.

Results

Of the eleven subjects who participated, six were in the tretinoin treatment group and five were in the placebo group. All eleven subjects' striae remained at grade 4. Therefore, these women showed a single grade of striae severity. Their ages ranged from eighteen to thirty-one years and the age of their striae from two weeks to thirteen years.

Results are summarized in Table I. Seven women lost weight and four gained weight in the study. At the time of the exit interview, to which ten subjects responded, equal numbers of women said that their striae improved and/or

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TABLE II
GRADING OF STRIAE DISTENSAE IN AN 8.5 BY 8.5 CM AREA

0=absent; no striae
1=mild; one striae≤1/2 cm wide
2=moderate; one or two striae>1/2 cm wide
3=moderate-severe; three to four striae any width
4=severe; more than four striae any width or too many to count

TABLE III
INTERRATER RELIABILITIES MATRIX FOR THE DERMATOLOGISTS' QUESTIONNAIRE

		DERMATOLOGIST		
		1	2	3
DERMATOLOGIST	1	1		
	2	0.43	1	
	3	0.62*	0.05	1

*$p<0.04$

remained the same regardless of their assigned treatment group. When the variables of subjects' "perception of improvement" and weight gain/loss were controlled, no difference between the groups existed. None of the subjects reported an exfoliative reaction with use of the 0.025 percent tretinoin cream. Several subjects reported mild pruritus, but placebo-treated subjects reported this as well.

The interrater reliabilities for the dermatologists' data are summarized in Table III. Only data from two of the three dermatologists correlated significantly: r=0.62 ($p<0.04$). An item analysis revealed that the color question had a significant correlation between these two dermatologists: r=0.84 ($p<0.001$). All other questionnaire items were not significantly correlated. When an analysis of variance F test was run separately for each of the dermatologists, only one dermatologist found a significant difference between the placebo-treated and tretinoin-treated groups. However, this result was in the direction of the placebo cream: F (11)=5.34, $p<0.04$. An item analysis, for this dermatologist's questionnaire, revealed percentage color change as significantly different: F (11)=6.797, $p<0.02$. Collapsing the questionnaire data across dermatologists revealed no difference between the tretinoin and placebo treatment groups: F (11)=2.15, ns. Therefore, the data generated from subjects and dermatologists showed no difference or improvement of the treated group over control subjects.

Comments

Striae distensae occur on the abdomen and/or breast in 90 percent of all pregnant women.[5] These skin changes were first described in the late 1800s.[7,8] Pregnancy is only one physiological condition in which striae can occur. Striae occur as sequelae to disease in a variety of other conditions, including Cushing's disease, diabetes mellitus (type I), Marfan's syndrome, obesity, use of topical and systemic steroids, and tuberculosis. Despite their numerous causes, the outward appearance is the same.[4,11] "Stretch marks," as they are commonly called, is really a misnomer. They may occur in the absence of obesity, such as in men and women experiencing malnutrition or toxic states. However, mechanical stress alone can often be implicated.[9,10] There are extrinsic factors (ie, mechanical stress), but more important are intrinsic factors (eg, hormones/steroids, genetic predisposition, and physiological stress) that interact to produce these lesions.

A considerable amount of study has been devoted to their histologic nature, ultrastructure, and biochemical composition.[6,9-11] There is debate over whether striae represent collagen-based or elastin-based damage to the dermis.[10,11] Several authors recently reported that the natural history of striae is reminiscent of dermal scarring.[9,10] After striae are formed, by any or all of these factors, an evolution occurs suggestive of the healing process of scar tissue.[10] Debate also continues over whether this is a collagen-based or an elastin-based injury-repair process.[10,11] Metabolic activity in striae remains increased over adjacent nonstriae tissue, which demonstrates the phenomenon of stress-remodeled connective tissue.[10] These lesions seem to be oriented in the direction of greatest stress/tension. Recently, retinoic acid-binding proteins have been identified on cultured dermal fibroblasts.[12] It has been suggested that receptors for retinoic acid, when stimulated, may decrease the number of fibroblast cells and diminished collagen synthesis in the dermis.[13,14] This is tretinoin's presumed mechanism of action, and not an irritant side effect.

Despite the extensive study of and cosmetic interest in striae distensae, an effective treatment has not yet been found. A recent literature search has confirmed only two studies suggesting efficacious treatment of any kind.[4,15]

Our double-blind prospective study examined the efficacy of tretinoin cream (0.025 percent) for the treatment of striae distensae in a small group of women. The previous study using 0.1 percent tretinoin cream had favorable, but anecdotal results, and subjects experienced irritation using this strength.[4] In our study, results showed that women could not reliably detect significant improvements in their lesions; two of three board-certified dermatologists could not detect a significant difference in improvement between treatment groups, and one dermatologist found the placebo treatment group significantly improved over the tretinoin-treated group.

Treatment compliance was not considered an issue for our subjects. Most subjects responded in the exit interview that they applied the treatment more than once per

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day (ie, twice). Also, treatment was applied over a greater area of skin. Usually their whole abdomen was treated.

Retinoid-induced irritation or edema is not considered the mechanism of action of skin lesion resolution. Research supports the influence of retinoids at the cellular level. Therefore, the lack of a local exfoliative reaction does not exclude the efficacy of the tretinoin medication. However, the results of this study did not dispel a dose-response relationship. A higher-dose tretinoin (0.1 percent) cream may be an effective treatment for striae distensae, but objective data are lacking.

Acknowledgment—Medication used in this study was provided by Ortho Pharmaceutical, Raritan, New Jersey.

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Cosmetic cream may prevent striae gravidarum

By Cheryl Guttman
Staff Correspondent

Paris — The development of pregnancy-related stretch marks can be reduced with the use of a topically applied cream containing 10 percent lactic acid with a soy peptide, according to the results of a randomized, vehicle-controlled, double-blind study presented at the World Congress of Dermatology.

The trial enrolled 78 pregnant women who were instructed to apply active cream or placebo to the hip, thigh, and periumbilical skin twice daily, continuing through the first month after delivery. Patients rated their responses and were evaluated by dermatologists for the presence and severity of stretch marks at baseline, and again after three months, five months, and study completion.

Less frequent, less evident marks

The results showed that stretch marks in women using the active cream developed later, less frequently, and were less clinically evident than in controls. The active cream was tolerated well, and patients were pleased with its efficacy and cosmetic properties, said Clarence de Belilovsky, M.D., dermatologist counsel, Expanscience Laboratories, Epernon, France.

"This randomized, double-blind, placebo-controlled clinical trial was done following a very strict, well-defined, relevant protocol, and its results show the cream fulfills the expectations of women who use it. The study demonstrated the cream provided a significant preventive effect on some components of stretch marks, and its efficacy was combined with good skin tolerance and cosmetic acceptability," said Chantal Gavaud-Kennedy, M.D., study investigator and private practice dermatologist.

The product tested is marketed by Expanscience Laboratories under the tradename Stretch Marks Double Action — Mustela 9 months. The study was performed by Institut d'Expertise Clinique, an independent research firm in Lyon, France, that performs safety and efficacy tests for cosmetics and pharmaceuticals. Dr. Gavaud-Kennedy serves as a clinical study investigator for IEC.

Focus on months three through five

Women were recruited for study participation at routine obstetrical exams occurring during months three through five of pregnancy. At study entry, the active cream and control groups were comparable with regard to mean age and mean weight. Limited stretch marks were present in three women in the placebo group and seven women in the active treatment group at baseline.

By five months after beginning use of the assigned study cream, stretch marks were present in 10 women in each treatment group. By the one-month postpartum visit, stretch marks had developed in an additional eight women using placebo compared with only four more women in the active cream group. Overall, new stretch marks developed in 40 percent of placebo users and 20 percent of the women in the active group.

Evaluations of the appearance of the stretch marks rated length, width, color, and relief on a scale of one to 10. At five months, the numerical data showed each of those features was less severe in the active treatment compared with control. At the final assessment, ratings for the four characteristics increased only minimally from the previous visit among women using the active cream, but worsened more markedly among the placebo-treated patients, and statistical analyses showed significant differences favoring the active cream for less redness and length.

The patient self evaluations of the lesions were consistent with the physician ratings. In addition, the vast majority of women using the active cream noted skin benefits of improved hydration, firmness, tonicity, elasticity, and suppleness, Dr. de Belilovsky said.

The active ingredients in the stretch-mark cream target synthesis of matrix proteins. When added to cultures of human skin cells, the soy peptides have been shown to stimulate fibroblast proliferation, and increase collagen and elastin synthesis by 60 percent and 30 percent, respectively, as well as the production of glycosoaminoglycans. The activity of the soy peptides is potentiated by the association of lactic acid.

Dr. Gavaud-Kennedy has no financial interest in the cream's developer, Expanscience Laboratories. CST